

PHAZIR Rx™

Satisfying GMP with Handheld Near-Infrared Analyzers in the Pharmaceutical Industry



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Identification and qualification of incoming pharmaceutical raw materials as well as properties of finished forms can be rapidly determined. Handheld near-infrared analyzers significantly enhance workflow and productivity.

Pharmaceutical manufacturing is a highly regulated industry as manufacturers of excipients, actives and finished forms need to conform to GMP. For example, in the European Union, EudraLex provides guidance for GMP practices and European Pharmacopeia (Ph. Eur.) recommends instrumentation and analysis protocols. In the United States, the FDA provides guidance for GMP and electronic record keeping under 21 CFR 210 and 11. Implementation of international harmonization has been effective in allowing the flow of materials across national borders. Given the increased demand for GMP and 100% inspection, the use of convenient and reliable handheld near-infrared (NIR) analyzers has proven to be a successful solution for inspection and compliance in the pharmaceutical industry.

From a production standpoint, following GMP has clear benefits. It is readily apparent that the quality and quantity of the active ingredient must be controlled. The “inactive” ingredients play an essential role in protecting and releasing the active ingredient under the appropriate conditions. Even low-concentration excipients may play a significant role in the release of the active. As the manufacturing process is tuned to producing millions of doses that perform within stringent limits, the ingredients must have predictable physical properties. Monitoring the raw materials and the finished products at-line during production runs allows processes to be implemented that ensure a more consistent product and increased efficiency.

Drug Discovery:	Stability of compound libraries.
Clinical trial:	Spot verification of placebo and active doses.
Receiving warehouse:	100% verification of receivables. Detection of common contaminants. Quantification of ingredient moisture content.
Dispensing:	100% Final verification of ingredients.
In process:	Reaction completion Determination of moisture content Solvent exchange monitoring Blend Uniformity
Finished Product:	Determination of ingredient ratios. Content uniformity. Thickness of tablet film coatings. Active ingredients and placebos in clinical trials.
Packaging:	Verification of packaging polymers. Determination of polymer thickness.
Post-production:	Degradation analysis of retained samples.

Table 1: Scenarios for handheld analyzers in the Pharmaceutical industry

Handheld analyzers are ideal for at-line measurements from drug development to analyzing retain samples. Table 1 outlines some scenarios.

Uses for handheld NIR analyzers

NIR analyzers have been used to measure ingredients, finished forms and packaging in the laboratory because they are rapid, non-destructive, and create little waste. Below, the differences between laboratory NIR and portable NIR implementations are discussed.

NIR

Near-infrared spectrometers are frequently used in the pharmaceutical industry for the identification and monitoring of solid dosage forms. The near infrared region contains information that relates to the structure of the molecules that compose the material. The near infrared region contains information that relates to the structure of the molecules that compose the material. Each molecule absorbs light in a characteristic pattern in the near-infrared region. The pattern depends on the vibrations that the light excites in the molecule. Some information about the physical properties appears as well. These patterns are used to deduce material identity and properties. The performance of portable NIR instruments is directly comparable in most applications to laboratory NIR instruments. The optical resolution, wavelength accuracy,

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wavelength range, signal to noise ratio, and linearity of the PHAZIR™ platform is matched to common qualitative and quantitative applications. The PHAZIR™ platform meets or exceeds the specifications of USP 1119.

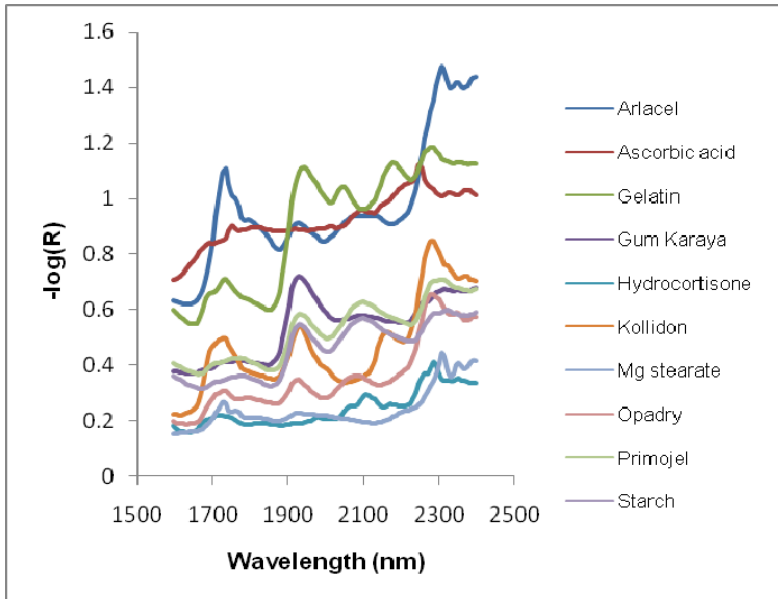


Figure 1. A subset of different pharmaceutical raw materials.

Portability, a significant difference

Portable NIR analyzers enable 100% incoming inspection. In contrast to laboratory instrumentation, there is no requirement for sampling, a chain of custody, labeling and transportation of the sample and releasing the original container. Because inspection processes with a handheld NIR analyzer are simplified, errors are reduced. Typical spectra are shown in Figure 1.

Portable NIR systems eliminate the need to move the container and allow inspection through closed polyethylene liners. Figure 2 demonstrates how the PHAZIR™ can be used. Moving the spectrometer reduces both errors and workplace hazards associated with moving large containers. Sampling through container liners avoids the release of dust and accidental chemical or biological contamination of the ingredient. Because the primary containment has not been breached, the material remains stable.

At the dispensing point, verifying the correct ingredient and qualities are critically important. Moisture, density, flowability and homogeneity are also important process parameters. All of these parameters can be verified at-line before the production process begins.

Rapid Deployment

Using the PHAZIR Rx™ for at-line measurements has the advantages of rapid deployment and simple integration into existing processes. The PHAZIR Rx™ can be calibrated in the laboratory by the QA/QC engineer and brought to the receiving warehouse or dispensing area for use by production technicians. Typical on-line and in-line instrumentation needs to be integrated tightly into the production environment, often needing to be designed-in or requiring modification to operations and the physical plant. The integration can make creating calibrations and calibration maintenance difficult. The PHAZIR Rx™ is software customizable; the same tool can be used by the engineers and technicians for many different applications.



Figure 2.

Identification

Because many actives and excipients are white powders, it can be difficult to visually verify or identify the materials. The PHAZIR Rx™ can be used in receiving to verify material supplied by the vendor. In many cases, identification can be performed without opening the bag containing the raw material. Handheld instrumentation has significant advantages for the identification process when the material must be kept aseptic or is received in large, difficult to move containers. Using near-infrared, the verification process can also include determination of moisture content. Unusually high or low moisture content can affect cost per weight, processability and storage of raw materials. Verification of identity at the receiving dock can reduce the size of the quarantine queue for receiving material.

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Figure 3. Handheld instrumentation can be brought to the material being identified. Polyethylene liners do not need to be opened for analysis.

The PharmaID™ application for the PHAZIR™ is an extensible starter kit for rapid raw materials identification. The application matches the measured NIR spectrum with a database of up to 10,000 representative spectra. Identification is based on the quality of several “best” matches. For materials that do not meet the minimum criteria for a match, the quality of match with the top three ingredients can be inspected. The results and the spectrum are recorded in an internal database with the user, time, date and user entered data. The contents of the database can be **securely** imported into a LIMS or exported to paper reports.

The PHAZIR Rx™ can be used in the dispensing process to verify material just before addition to the hopper for a granulator or tablet press. Because the visual inspection of the material being added is unreliable, the potential for error in adding improper material to a granulator or tablet press hopper is relatively high. Utilizing a PHAZIR Rx™ as a final verification step can reduce errors. Measurement and analysis time is rapid, typically less than 5 seconds and the result is displayed on the device for operator convenience. The internal 21 CFR 11 compliant database records the spectrum, result and user-entered identifiers.

Qualification

Both excipients and finished forms have quantitative properties that determine whether the material is in-or-out-of-specification. At-line verification of product can reduce the costs associated with out-of-specification specification lots to be produced. The PHAZIR Rx™ can run applications that display up to eight quantitative values from a single measurement.

As an example, for raw materials, near-infrared provides a rapid and accurate way of assessing moisture content. Water in crystalline hydrates and anhydrous materials, such as lactose and potassium hydrogen phosphates can be very accurately assessed. Crystalline form, compressibility, density, average particle size and contaminants can also be assessed in powders. Tablets can be characterized by the major components, compression, moisture, crushing strength and dissolution rate. Film and sugar-coated tablets, granules and pellets can be assessed for coating thickness, as shown in Figure 4 and Figure 5. In the NIR, even colored coatings have sufficient contrast between absorbing regions and transparent regions to allow accurate assessment of thickness. Gelatin, and other types of capsules, has similar characteristics to tablet coatings. Simultaneous determination of capsule composition and filler composition can be performed.



Figure 4: Ecotrin™ Tablets

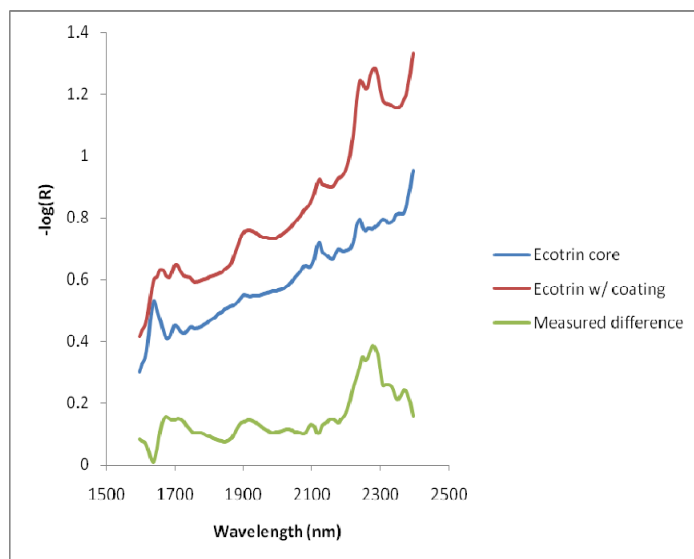


Figure 5: Ecotrin™ Coating Spectrum

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Regulatory Compliance

The PHAZIR Rx™ is designed for use by the pharmaceutical industry. Installation, operational and performance qualification (IQ, OQ and PQ) procedures are implemented using the standards specified by USP 1119. The Rx 21 CFR part #11 compliance package provides logins, passwords, electronic records of results, spectra, electronic signatures and integration into LIMS systems to satisfy the FDA electronics records requirements.

- 10/OQ/PQ Manual
- 21 CFR Part 11 Compliance
- ISO 9000 Quality System
- USP 1119 NIR qualification protocol
- Traceable Standards

Preferred configuration (includes P/N)

- PHAZIR Rx™ 1624
- Liquids adapter
- Extra battery
- PHAZIR Rx-MG™
- 21 CFR 11 package
- USP 1119 standards rental
- Starter library (bags)
- Starter library (vials)

Features

- Rapid identification and quantification. Typically < 3 seconds.
- Bright LCD display for displaying spectra and results.
- Sampling through glass vials or plastic bags
- Interchangeable liquids and solids analysis with a simple click-on adapter
- 10-hour quick-change battery
- Solids and optional liquids analysis